Received: 25 December 2019 | Accepted: 26 December 2019

DOI: 10.1111/liv.14354

REVIEW ARTICLE

Liver INTERNATIONAL WILEY

New drugs for non-alcoholic steatohepatitis

Ana-Carolina Cardoso[1,2] | Claudio de Figueiredo-Mendes[3] | Cristiane A. Villela-Nogueira[1,2] | Arun J. Sanyal[4]

[1]Hepatology Division, Clementino Fraga Filho University Hospital, Rio de Janeiro, Brazil

[2]School of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[3]Hepatology Division, General Hospital of Santa Casa do Rio de Janeiro, Rio de Janeiro, Brazil

[4]Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

Correspondence
Ana Carolina Cardoso, Hepatology Division, Clementino Fraga Filho University Hospital, School of Medicine, Federal University of Rio de Janeiro, Brazil.
Email: acfcardoso@gmail.com

Funding information
Conselho Nacional de Desenvolvimento Científico e Tecnológico de Pesquisa (CNPq); e Fundação Carlos Chagas de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ); NIH, Grant/Award Number: 105961

Handling Editor: Luca Valenti

Abstract

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in Western countries. At present the safest and most effective first-line therapy for the management of non-alcoholic steatohepatitis (NASH) is lifestyle modification with diet and exercise. However, long-term adherence to lifestyle modification is rare in the target population, leading to progression of liver disease and its complications such as cirrhosis and hepatocellular carcinoma. Thus, new drugs that focus mainly on the pathogenesis of NASH to target inflammation and fibrogenesis are under investigation. This mini-review summarizes the results of pivotal finalized phase 2 studies, and provide an outline of ongoing phase 2 and phase 3 studies.

1 | INTRODUCTION

Despite the high prevalence and importance of non-alcoholic fatty liver disease (NAFLD), the incorrect idea that the progression of this disease is usually benign has considerably limited the development of drugs for non-alcoholic steatohepatits (NASH). With the awareness that NAFLD can progress to advanced stages of liver injury and is associated with possible complications such as hepatocellular carcinoma and hepatic failure, there has been a significant increase in the number of studies investigating new drugs for more effective management of liver disease. Although there are about 196 agents being evaluated for the treatment of NASH, none of these drugs has been approved to treat this disease so far. However, many phase 2 and 3 trials are ongoing and a new chapter is expected in NASH treatment in the near future (Table 1).

1.1 | Obeticholic acid

Obeticholic acid (OCA) is derived from the primary human bile acid, chenodeoxycholic acid, which stimulates the farnesoid X nuclear receptor (FXR) in humans.[1] OCA stimulates FXR activity approximately 100-fold more intensely than chenodeoxycholic acid, and is highly

Abbreviations: NAFLD, Non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OCA, Obeticholic acid; FXR, farnesoid X nuclear receptor; NAS, non-alcoholic fatty liver disease activity score; CVC, Cenicriviroc; CCR2, chemokine receptor type 2; CCR5, chemokine receptor type 5; TZD, thiazolidinedione; MPC, mitochondrial pyruvate carrier; PPAR, peroxisome proliferator activated receptor; T2D, type 2 diabetes; FGF19, fibroblast growth factor 19; MRI-PDFF, MRI-proton density fat fraction; ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; THR β, thyroid hormone receptor β; HFF, hepatic fat fraction; AST, aspartate aminotransferase; TXR, Tropifexor; Aramchol, Arachidyl-amido cholanoic acid; SCD1, Stearoyl-CoA desaturase 1, MUFAs, monounsaturated fatty acids; ASK1, apoptosis signal-regulating kinase 1.

selective with minimal activity to G protein-coupled bile acid receptor, another bile acid receptor.[1] The FXR nuclear receptor is expressed in the liver, intestines, adrenal glands and kidneys and plays an important role in the synthesis and enterohepatic circulation of bile acids.[2] Activation of FXR in the ileum also inhibits the uptake of bile acids by downregulating the sodium-dependent bile acid transporter. Its main function is to regulate cholesterol lipoprotein and bile acid metabolism to modulate immuno-inflammatory and fibrogenic responses.[2] Other important function of farnesoid X receptor activation is to reduce bile acid synthesis by inhibiting the conversion of cholesterol to bile acids.

The main trials evaluating OCA are the FLINT trial, a phase 2b study[3] and the ongoing REGENERATE phase 3 study.[4] The FLINT trial was a multi-centre, double-blind, placebo-controlled, randomized clinical trial in the USA in biopsy-proven NASH patients without cirrhosis with a non-alcoholic fatty liver disease activity score (NAS) ≥4, with at least 1 point in each component of the score. This study assessed treatment with 25 mg daily of oral OCA compared to placebo for 72 weeks. The primary outcome was improvement in centrally scored liver histology defined as a decrease of at least 2 points in NAS without worsening of fibrosis from baseline to the end of treatment. A total of 141 patients were randomly assigned to receive OCA and 142 to receive placebo in this trial. Forty-five per cent of the 110 patients in the OCA group who were scheduled to undergo biopsies at baseline and at 72 weeks had improved liver histology compared to 21% of the 109 patients in the placebo group (relative risk 1.9, 95% CI 1.3-2.8; $P = .0002$). Twenty-three per cent of the 141 patients in the OCA group developed pruritus compared to only 6% of 142 in the placebo group. The conclusion of the FLINT trial was that OCA improved the histological features of NASH, but further studies were needed to determine the long-term benefits and safety of this agent.

The main objectives of REGENERATE, an ongoing phase 3 global study are to compare the effects of OCA to placebo for histological improvement and liver-related clinical outcomes in patients with NASH and stage 2 or 3 liver fibrosis. A liver biopsy is obtained at screening, at 18 and 48 months, and at the end of study. The estimated completion date of this study is October 2022. This study has three arms and patients are randomized 1:1:1 as follows: OCA 10 mg, OCA 25 mg daily and placebo. The primary endpoints are the proportion of OCA-treated patients vs placebo who achieve an improvement of at least one stage in liver fibrosis with no worsening of NASH or the proportion of OCA-treated patients compared to placebo with a resolution of NASH and no worsening of liver fibrosis. All-cause mortality and liver-related clinical outcomes will also be evaluated as secondary endpoints. The results of the interim 18-month analysis[5] showed that 1968 patients with stage F1-F3 fibrosis were enrolled and received at least one dose of treatment. Nine hundred and thirty-one patients with stage F2-F3 fibrosis were included in the primary analysis (311 in the placebo group, 312 in the OCA 10 mg group and 308 in the OCA 25 mg group). The endpoint for the improvement in fibrosis was achieved by 37 (12%) patients in the placebo group, 55 (18%) in the OCA 10-mg group ($P = .045$), and 71 (23%) in the OCA 25-mg group ($P = .0002$). NASH resolution was not achieved in any patient. As reported previously, the main adverse event was pruritus with 28% in the 10-mg group and 51% in the 25-mg group compared to 19% in the placebo group. The evaluation of clinical outcomes is ongoing.

Key Points

- Despite the high prevalence and potential consequences of NASH, there are currently no approved treatments for this disease
- There are many new drugs in the pipeline
- Specific medications can potentially be used to target inflammation and fibrosis
- The main new drugs under investigation are agonist or inhibitors of specific receptors
- The new drugs will likely be used in combination to increase their effectiveness

TABLE 1 List of drugs currently being evaluated in phases 2 and 3 clinical trials

Drug(s)	Mechanism of action	Phase in clinical trial	Trial identification
Obeticholic acid	FXR agonist	III	NCT02548351
Elafibranor	PPAR-α/δ agonist	III	NCT02704403
Cenicriviroc	CCR2/CCR5 inhibitor	III	NCT03028740
MSDC-0602K	MPC inhibitor	IIb	NCT02784444
NGM282	FGF19 analogue	IIb	NCT03912532
Saroglitazar	PPAR-α/γ agonists	II	NCT03061721
Resmetirom	THR-ß agonist	III	NCT03900429
Tropifexor	FXR agonist	IIb	NCT02855164
Aramchol	SCD1 inhibitor	III	3rd quarter 2019
Selonsertib	ASK1 inhibitor	III	NCT03053050

Abbreviations: ASK1, apoptosis signal-regulating kinase 1; CCR, C-C chemokine receptor; FGF, fibroblast growth factor; FXR, farnesoid X receptor; MPC, mitochondrial pyruvate carrier; PPAR, peroxisome proliferator-activated receptor; SCD-1, Stearoyl-CoA desaturase 1; THR-ß, thyroid hormone receptor ß.

1.2 | Elafibranor

Elafibranor is a peroxisome proliferator-activated receptor alpha-delta α/δ agonist. It regulates lipid and insulin metabolism, two key components in the pathophysiology of NAFLD and NASH. The GOLDEN study[6] was a phase 2b multi-centre (Europe and USA), double-blind, randomized controlled trial comparing elafibranor 80 mg and 120 mg daily to placebo for 52 weeks, including 276 patients with biopsy-proven, noncirrhotic NASH with NAS ≥3 and ≥1 point for each component in the score. Reversal of NASH, defined as the absence of at least 1 of either steatosis, ballooning or inflammation without progression to bridging fibrosis or cirrhosis, was not achieved. However, NASH resolved without fibrosis worsening in a higher proportion of patients in the 120-mg elafibranor group vs the placebo group (19% vs 12%; odds ratio = 2.31; P = .045), based on a post hoc analysis for the modified definition. In post hoc analyses of patients with non-alcoholic fatty liver disease activity score ≥4 (n = 234), elafibranor 120 mg resolved NASH in larger proportions of patients than placebo based on the protocol definition (20% vs 11%; odds ratio = 3.16; P = .018) and the modified definitions (19% vs 9%; odds ratio = 3.52; P = .013). Patients with NASH resolution after receiving elafibranor 120 mg had reduced liver fibrosis stages compared with those without NASH resolution (mean reduction of 0.65 ± 0.61 in responders for the primary outcome vs an increase of 0.10 ± 0.98 in nonresponders; P < .001). Liver enzymes, lipids, glucose profiles, and markers of systemic inflammation were significantly reduced in the elafibranor 120-mg group vs the placebo group. Elafibranor was well tolerated and did not cause weight gain or cardiac events, but did produce a mild, reversible increase in serum creatinine.[6]

RESOLVE-IT (https://clinicaltrials.gov/ct2/show/NCT0270443) is an ongoing phase 3 study that will include 2,000 NASH patients with NAS ≥4, with ≥1 of each component of the score and F1-F3 fibrosis. The primary outcome is histological improvement, defined as the resolution of NASH without worsening of fibrosis at 72 weeks with a composite outcome that will evaluate all-cause mortality, cirrhosis and "liver-related clinical outcomes" at 4 years. Results are due in December 2021.

1.3 | Cenicriviroc

Cenicriviroc (CVC) is an oral, dual antagonist of chemokine receptor type 2 (CCR2) and type 5 (CCR5), located on Kupffer cells and hepatic stellate cells.[7] This mechanism of action drives the molecular engines that drive NASH via blockade of overactive inflammatory signalling and disruption of signalling that activates stellate cells, targeting both inflammation and fibrogenesis. CVC is administered in 150 mg daily tablets, since it has a long plasma life of 30-40 hours. CENTAUR[8] was a phase 2b, 24-month study that included 189 patients randomized 2:1:1 in three arms as follows: arm A with continuous administration of 150-mg CVC for 24 months, arm B with placebo for 12 months followed by an additional 12 months of CVC and arm C with placebo for 24 months. Included patients underwent a protocol liver biopsy at baseline, 12 months and at the end of 24 months. Eligible patients had biopsy-proven NASH with an NAS ≥4 and stage 1-3 fibrosis. The primary outcome of a ≥2 point decrease in NAFLD activity score with no worsening of fibrosis at 1 year was not achieved. However, a key secondary outcome was the improvement in liver fibrosis without worsening of NASH, which was achieved in 20% from the treatment group as well as lower levels of interleukin-6, C-reactive protein and fibrogen in this group.[8]

Currently, AURORA (https://clinicaltrials.gov/ct2/show/NCT03028740), a randomized, double-blind, placebo-controlled, multi-centre phase 3 study is ongoing to evaluate the efficacy and safety of CVC for the treatment of moderate to severe liver fibrosis in adults with NASH. The overall aim is to include 2,000 patients with NASH and F2-F3 fibrosis in a 2:1 CVR to placebo ratio in each of the arms. The first part of this study was designed to determine the superiority of CVC for the improvement of at least one stage of fibrosis without worsening of NASH after 12 months of CVC. The aim of the second part of this study is to evaluate the composite endpoint of histopathological progression to cirrhosis, liver-related clinical outcomes, and all-cause mortality over 5 years. A liver biopsy will be performed at baseline, at 12 months and at the end of this study, at month 60.

1.4 | MSDC-0602K

The first-generation insulin sensitizer pioglitazone, a thiazolidinedione (TZD), improved NASH but had many side effects which have limited its use.[9]

MSDC-0602K is a second-generation insulin sensitizer. It is an inhibitor of the mitochondrial pyruvate carrier (MPC) with minimal peroxisome proliferator activated receptor γ (PPAR) binding. Initial studies showed that MSDC-0602 could increase lipid oxidation and reduce de novo lipid synthesis and gluconeogenesis in the liver, both in vivo and in vitro, without the side-effects of first-generation insulin sensitizers.[9]

The phase 2b 52-week double-blind study evaluating MSDC-0602K included 392 biopsy-confirmed NASH (NAS >4, ≥1 in each component) patients with histological evidence of F1-F3 fibrosis (at least 50% F2/F3). Half of the patients had controlled type 2 diabetes (T2D). The primary endpoint was hepatic histological improvement of ≥2 points in NAS with a ≥1-point reduction in either ballooning or lobular inflammation, and no increase in fibrosis at 12 months. The secondary endpoints included improvement in NAS without worsening fibrosis, resolution of NASH and a reduction in fibrosis. The exploratory endpoints included changes in insulin sensitivity, liver injury and liver fibrosis markers. All patients were randomized to receive a single daily dose of placebo or 62.5 mg, 125 mg or 250 mg of the compound. Although analysis of MSDC-0602K study data did not show any statistically significant effects on primary or secondary liver histology endpoints, the effects on the non-invasive measures of liver cell injury and glucose metabolism were identified. The incidence of hypoglycemia and PPARγ-agonist-associated

events such as oedema and fractures were similar in the placebo and MSDC-0602K groups. The authors concluded that further studies were needed to clarify the results obtained.[10]

1.5 | NGM282

NGM282 is an engineered analogue of FGF19, a hormone that regulates bile acid synthesis, glucose homoeostasis and energy homoeostasis. Previous studies have shown that mice expressing FGF19 have an increased metabolic rate, decreased adiposity and increased insulin sensitivity with no increase in the hormones most often associated with an increase in metabolic rate. However, the therapeutic potential of fibroblast growth factor 19 (FGF19) has been limited by its hepatocarcinogenicity.[11]

NGM282, a nontumorigenic variant of FGF19 was evaluated in a randomized, double-blind, placebo-controlled, phase 2 study, that included patients with biopsy-proven non-alcoholic steatohepatitis. Patients were assigned (1:1:1) to receive either 3 mg or 6 mg of subcutaneous NGM282 or placebo. The primary endpoint was an absolute change in liver fat content from baseline to week 12. Responders were patients who achieved at least a 5% reduction in absolute liver fat content measured by MRI-proton density fat fraction (MRI-PDFF).[11]

At 12 weeks, 20 (74%) patients in the 3-mg group and 22 (79%) in the 6-mg group achieved the primary endpoint vs. two (7%) in the placebo group. Side effects such as injection site reactions (34%); diarrhoea (33%), abdominal pain (18%) and nausea (17%) were diagnosed in 76/82 (93%) patients and were more frequent in the NGM282 groups. No life-threatening events or patient deaths occurred during this study. The authors concluded that NGM282 is associated with a reduction in liver fat content with an acceptable safety profile in patients with non-alcoholic steatohepatitis.[11]

1.6 | Saroglitazar

Saroglitazar, a dual-peroxisome proliferator-activated receptor agonist, has been shown to improve lipid and glycemic parameters through PPAR-α and γ agonist actions respectively (predominant PPAR-α and moderate PPAR-γ actions).

Recently, a phase-2, prospective, multi-centre, double-blind, randomized trial was performed to determine the efficacy and safety of saroglitazar magnesium compared to placebo in patients with NAFLD/NASH. A total of 106 adult subjects who had alanine aminotransferase (ALT) ≥50 U/L and body mass index ≥25 kg/m^2 were randomized in a 1:1:1:1 ratio to receive 1 mg, 2 mg or 4 mg of saroglitazar and placebo. The primary endpoint was the percentage of change in ALT levels from baseline to week 16 in the saroglitazar vs placebo groups. The secondary endpoints included the proportion of patients with ≥50% reduction in ALT levels and change in liver fat content (measured by MRI-PDFF) from baseline to week 16 in the saroglitazar vs placebo groups. The primary endpoint was achieved in all three groups with saroglitazar. A significant reduction in mean ALT from baseline to week 16 was observed with saroglitazar 1 mg (−27.3%), 2 mg (−33.1%) and 4 mg (−44.3%) vs placebo (4.1%) ($P < .001$ for all). A significantly higher proportion of patients had ≥50% reduction in mean ALT from baseline to week 16 with saroglitazar 4 mg compared to placebo (51.8% vs 3.5%; $P < .0001$). At week 16, saroglitazar 4 mg resulted in a significantly higher reduction in HOMA-IR, triglycerides, total cholesterol and AST to Platelet Ratio Index (APRI) than placebo ($P < .05$ for all). A significantly higher percentage of patients had >30% reduction in liver fat content with saroglitazar 4 mg than with placebo (40.7% vs 8%, $P = .006$). There was no significant change in the percentage of body weight between saroglitazar 4 mg and placebo (1.88% vs 0.28%, $P = .9$) and overall, saroglitazar was well tolerated.[12]

1.7 | Resmetirom (MGL-3196)

The thyroid hormone receptor β (THR β) is highly expressed in hepatocytes and is responsible for regulating the metabolic pathways in the liver that are frequently impaired in NAFLD and NASH.[13] Resmetirom (MGL-3196, Madrigal Pharmaceuticals Inc), a highly selective THR β agonist, has been developed to target dyslipidemia but has also been shown to reduce hepatic steatosis in fat-fed rats, improving insulin sensitivity, promoting liver regeneration and reducing apoptosis.[14]

This double-blind, randomized, placebo-controlled phase 2 study included patients with biopsy proven NASH and ≥10% liver steatosis. The primary outcome was the percentage of change from baseline in hepatic fat fraction (HFF) assessed by MRI-PDFF at 12 weeks for Resmetirom vs placebo. Eligible liver biopsies included stage 1-3 fibrosis with an NAFLD activity score of at least 4, including a score of at least 1 in each component according to the NASH clinical research network scoring system.[15]

A total of 125 patients were included from October 2016 to July 2017 from 25 medical centres in the USA. A statistically significant improvement was found at 12 weeks in the relative decrease in liver fat in patients treated with Resmetirom compared to placebo. Statistically significant reductions were also observed in ALT and AST levels in Resmetirom-treated patients. Statistically significant effects in the reduction of atherogenic lipids, lipo-protein(a), markers of inflammation and fibrosis were also found compared to placebo as well as improvements in NASH on liver biopsy. The evaluation of more advanced NASH was limited by the relatively low baseline NAS and the few patients with advanced stages of fibrosis. Resmetirom was well tolerated even if it was associated with an increase in gastrointestinal adverse events. These adverse events were self-limited and did not result in study withdrawal.[15]

A phase 3 in patients with NASH and fibrosis is now recruiting (https://clinicaltrials.gov/ct2/show/NCT03900429).

1.8 | Tropifexor (LJN-452)

Tropifexor (TXR) is a highly potent, nonbile acid FXR agonist that induces target genes at very low doses in vitro and in vivo, and

has been shown to be effective in pre-clinical models of NASH.[16] The tolerability and safety of TXR was shown to be favourable in a phase 1 study in healthy volunteers (unpublished results). A phase 2 adaptive design study (FLIGHTFXR) in patients with NASH is ongoing (https://clinicaltrials.gov/ct2/show/NCT02855164). In addition, a recent randomized, double-blind, multi-centre, phase 2b study is evaluating the safety and efficacy of a combination of TXR and cenicriviroc in patients with biopsy-proven NASH and liver fibrosis (stages F2/F3). This study includes a 48-week treatment period and 4 weeks of follow-up.[17]

1.9 | Arachidyl amido cholanoic acid (Aramchol)

Arachidyl amido cholanoic acid, a cholic-arachidic acid conjugate, targets Stearoyl-CoA desaturase 1 (SCD1), inhibiting the synthesis of monounsaturated fatty acids (MUFAs), the major fatty acid of triglycerides, cholesteryl esters and membrane phospholipids.[18] Aramchol (400 and 600 mg) was tested in biopsy-proven NASH patients without cirrhosis in a 52-week phase 2b trial (2018) to evaluate their effect on hepatic triglyceride content using MRI spectroscopy (https://clinicaltrials.gov/ct2/show/NCT02279524). A recent double-blind, randomized, placebo-controlled trial tested the efficacy of 12 weeks of treatment with aramchol vs placebo in HIV-associated NAFLD.[19] Fifty patients with HIV-associated NAFLD, defined by MRI-PDFF ≥5%, were randomized to receive either aramchol 600 mg daily (n = 25) or placebo (n = 25) for 12 weeks. This study concluded that aramchol did not reduce hepatic fat or change body fat and muscle composition based on an MRI assessment in patients with HIV-associated NAFLD.[19]

1.10 | Selonsertib (SEL, GS-4997)

Selonsertib is an inhibitor of apoptosis signal-regulating kinase 1 (ASK1) that causes apoptosis and fibrosis. An open-label phase 2 trial evaluating NASH patients with moderate and severe liver fibrosis identified a regression in fibrosis and other parameters of liver injury.[20] Therefore, phase 3 trials evaluating NASH patients with stage 3 fibrosis (http://www.natap.org/2019/HCV/050819_01.htm) – STELLAR 3 – or cirrhosis (http://www.natap.org/2019/HCV/022719_01.htm) – STELLAR 4 – were initiated. Because STELLAR 4 did not reach the primary endpoint (at least one-point reduction in fibrosis score, without worsening of NASH at 48 weeks) it was discontinued and the STELLAR program was cancelled.

ACKNOWLEDGEMENTS

Cristiane A Villela-Nogueira receives research grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico de Pesquisa (CNPq), e Fundação Carlos Chagas de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Brazil. The authors acknowledge funding from NIH project RO1 DK 105961 to Arun J. Sanyal

CONFLICTS OF INTEREST

Ana Carolina Cardoso: None. Claudio de Figueiredo Mendes: None. Cristiane A Villela-Nogueira is the principal investigator of the AURORA study at Federal University of Rio de Janeiro site in Brazil.

Arun Sanyal: Dr Sanyal is the President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect and Galmed. He has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Jannsen, Gilead, Terns, Birdrock, Merck, Valeant, Boehringer-Ingelheim, Lilly, Hemoshear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exhalenz and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Zydus, Nordic Bioscience, Albireo, Prosciento, Surrozen and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, Astra Zeneca, Malinckrodt, Cumberland and Novartis. He receives royalties from Elsevier and UptoDate.

ORCID

Ana-Carolina Cardoso https://orcid.org/0000-0002-4552-8453
Claudio de Figueiredo-Mendes https://orcid.org/0000-0001-8668-4236
Cristiane A. Villela-Nogueira https://orcid.org/0000-0003-1355-2368
Arun J. Sanyal https://orcid.org/0000-0001-8682-5748

REFERENCES

1. Pellicciari R, Costantino G, Camaioni E, et al. Bile acid derivatives as ligands of the farnesoid X receptor. Synthesis, evaluation, and structure-activity relationship of a series of body and side chain modified analogues of chenodeoxycholic acid. *J Med Chem*. 2004;47(18):4559-4569.
2. Jhaveri MA, Kowdley KV. New developments in the treatment of primary biliary cholangitis - role of obeticholic acid. *Ther Clin Risk Manag*. 2017;13:1053-1060.
3. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385(9972):956-965.
4. Ratziu V, Sanyal AJ, Loomba R, et al. REGENERATE: Design of a pivotal, randomised, phase 3 study evaluating the safety and efficacy of obeticholic acid in patients with fibrosis due to nonalcoholic steatohepatitis. *Contemp Clin Trials*. 2019;84:105803.
5. Younossi ZM, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2019.
6. Ratziu V, Harrison SA, Francque S, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-alpha and -delta, induces resolution of nonalcoholic steatohepatitis without fibrosis. *Worsening. Gastroenterology*. 2016;150(5):pp. 1147-1159. e1145.
7. Lefebvre E, Moyle G, Reshef R, et al. Antifibrotic effects of the dual CCR2/CCR5 antagonist cenicriviroc in animal models of liver and kidney fibrosis. *PLoS ONE*. 2016;11(6):e0158156.
8. Friedman S, Sanyal A, Goodman Z, et al. Efficacy and safety study of cenicriviroc for the treatment of non-alcoholic steatohepatitis in adult subjects with liver fibrosis: CENTAUR Phase 2b study design. *Contemp Clin Trials*. 2016;47:356-365.

9. Colca JR, McDonald WG, Adams WJ. MSDC-0602K, a metabolic modulator directed at the core pathology of non-alcoholic steatohepatitis. *Expert Opin Investig Drugs*. 2018;27(7):631-636.
10. Harrison SA, Alkhouri N, Davison BA, et al. Insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase IIb study. *J Hepatol*. 2019. [Epub ahead of print]. https://doi.org/10.1016/j.jhep.2019.10.023
11. Harrison SA, Rinella ME, Abdelmalek MF, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2018;391(10126):1174-1185.
12. Gawrieh S, Noureddin M, Loo NM, et al. A phase 2, prospective, multicenter, double-blind, randomized, study of saroglitazar magnesium 1 mg, 2 mg or 4 mg versus placebo in patients with non-alcoholic fatty liver disease and/or nonalcoholic steatohepatitis (EVIDENCES IV). *Hepatol Commun*. 2019;LT;10.
13. Sinha RA, Bruinstroop E, Singh BK, Yen PM. Nonalcoholic fatty liver disease and hypercholesterolemia: roles of thyroid hormones, metabolites, and agonists. *Thyroid*. 2019;29(9):1173-1191.
14. Vatner DF, Weismann D, Beddow SA, et al. Thyroid hormone receptor-beta agonists prevent hepatic steatosis in fat-fed rats but impair insulin sensitivity via discrete pathways. *Am J Physiol Endocrinol Metab*. 2013;305(1):E89-100.
15. Harrison SA, Bashir MR, Guy CD, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet*. 2019;394(10213):2012-2024.
16. Tully DC, Rucker PV, Chianelli D, et al. Discovery of tropifexor (LJN452), a highly potent non-bile acid FXR agonist for the treatment of cholestatic liver diseases and nonalcoholic steatohepatitis (NASH). *J Med Chem*. 2017;60(24):9960-9973.
17. Pedrosa M, Seyedkazemi S, Francque S, et al. A randomized, double-blind, multicenter, phase 2b study to evaluate the safety and efficacy of a combination of tropifexor and cenicriviroc in patients with nonalcoholic steatohepatitis and liver fibrosis: study design of the TANDEM trial. *Contemp Clin Trials*. 2019;88:105889.
18. Leikin-Frenkel A, Gonen A, Shaish A, et al. Fatty acid bile acid conjugate inhibits hepatic stearoyl coenzyme A desaturase and is non-atherogenic. *Arch Med Res*. 2010;41(6):397-404.
19. Ajmera VH, Cachay E, Ramers C, et al. MRI assessment of treatment response in HIV-associated NAFLD: a randomized trial of a stearoyl-coenzyme-A-desaturase-1 inhibitor (ARRIVE trial). *Hepatology*. 2019;70(5):1531-1545.
20. Loomba R, Lawitz E, Mantry PS, et al. The ASK1 inhibitor selonsertib in patients with nonalcoholic steatohepatitis: a randomized, phase 2 trial. *Hepatology*. 2018;67(2):549-559.

How to cite this article: Cardoso AC, de Figueiredo-Mendes C, Villela-Nogueira CA, Sanyal AJ. New drugs for non-alcoholic steatohepatitis. *Liver Int*. 2020;40(Suppl. 1):96–101. https://doi.org/10.1111/liv.14354